# Preliminary Review of Vaccine Vial Monitors (VVMs)

Version 11b – 9 March 2009

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## 1. Purpose

In 2008, the department of Immunizations, Vaccines, and Biologicals (IVB) of the World Health Organization (WHO) created the Technologies and Logistics Advisory Committee (TLAC) to become one among a family of related advisory committees in the field of vaccines and immunization. [1, 2, 3, 4] These committees were reorganized in recent years following the recommendations of an external review [5] which identified and recommended … :

- "The critical position of research and evidence in the work of IVB …"
- "That the independence of advisory committees be affirmed as essential for their success, *including the independence of committees* from donors and from the advocacy functions of WHO itself." [italicized underlining added]

Similar to other WHO immunization advisory committees, TLAC and its members are charged to: [6]

- " … provide[s] policy and technical advice in a specific area, based on solid scientific evidence, …" [p. 5]
- " … consult[s] widely as and when necessary …" [p. 5]
- " … provide WHO with rigorous, well-considered advice and recommendations …" [p. 12]
- " … provide[s] the evidence on which such conclusions and recommendations are based … " [p. 5]
- " … address or review specific issues ahead of meetings in order to increase the effectiveness pf TLAC deliberations by providing evidence-based information and options … " [p. 13]

WHO requested TLAC consideration of two major topics at its first meeting in September, 2008.[7] These included a proposed new strategy to take certain vaccines, particularly for prevention of hepatitis B infection, "out of the cold chain" ("OCC") at the periphery of immunization programs, in order to reduce freeze damage within it and for other potential benefits.[8]

The other topic concerned a needed revision of WHO's existing Multi-dose Vial Policy ("MDVP") and other guidelines for how long vaccines may be administered once their vials are opened. New vaccine packaging and formulations are rendering obsolete the existing rules.

Referring to studies proposed for the OCC initiative, among the specific questions asked of TLAC were:

> "Will the study, as proposed, provide assurance that hepatitis B vaccine can be transported and used OCC?
>
> "Will it be sufficient to look at potency, both *in vivo* and *in vitro*, and impact on shelf life, after exposure to 45°C until all of the VVMs reach their discard points, once the correlation of potency and VVM color change has been demonstrated above 37°C?"

A Vaccine Vial Monitor (VVM) is a specific type of time-temperature indicator (TTI) that is applied directly to individual single-dose and multi-dose vaccine vials, and would play a key role in any new policy recommendations regarding OCC and MDVP. Consequently, TLAC

undertook a review of VVM technology by an *ad hoc* team comprised of members Jonathan S. Colton (Georgia Institute of Technology) and Bruce G. Weniger, TLAC Chair (US Centers for Disease Control and Prevention). [a] The purpose was to examine its underlying scientific evidence and data on VVMs and to educate fellow TLAC members in preparation for future policy discussions.

The review included examination of documents furnished from WHO and elsewhere, as well as those gathered from the published literature and online sources. Also consulted were experts in national regulatory authorities, industry, and academia familiar with the VVM technology and relevant product development, regulatory, scientific, and manufacturing issues.

## 2. Background on VVMs

### *2.1 History*

TTIs are devices that monitor the cumulative exposure of both time and temperature in order to measure or predict the degradation of temperature-sensitive products. In 1979, as a consequence of good experience with other TTIs at higher levels of the cold chain (e.g., vaccine storage boxes), WHO conceived the concept for VVMs in order to be able to extend such monitoring to the periphery. [9, 10] Over the 1980s and until the mid-to-late 1990s, several different TTI technologies were pursued by several companies with developmental initiative from PATH and some financing from the U.S. Agency for International Development (USAID). [9, 10, 11]

However, by 1998 only one company remained in the effort (Lifelines Technology, Inc., subsequently becoming Temptime Corporation) with its HEATmarker™ VVM, based on the chemistry of diacetylene polymers.

The first VVM was developed for the freeze-tolerant but highly heat-sensitive oral polio vaccine (OPV) and first applied in 1996 to marketed vaccine vials used in the Expanded Programme on Immunization (EPI). Over the past decade, Temptime Corporation has remained the sole world manufacturer of VVMs for use on vaccines in the EPI. Given this single-source status, for convenience in this review the term "VVM" – unless indicated otherwise – is used to refer specifically to the trademarked HEATmarker TTI applied to WHO/EPI vaccines.

A particularly thorough history of the remarkable perseverance and ultimate triumph in the long development process that brought the innovative vision of a VVM to fruition is told in reference 9. Additional background is available in various promotional materials and resources. [12, 13, 14, 15, 16, 17, 18]

WHO and the United Nations Children's Fund (UNICEF) strongly support -- and indeed now mandate -- the use of VVMs on vaccines procured through UNICEF to help ensure that administered product has not been damaged by heat, and to reduce wastage when still-potent

[a] For convenience to TLAC members, Jonathan's draft summary of VVMs was distributed on 27 February 2009, well in advance of TLAC's second meeting on 11-12 March 2009. Bruce's VVM review was completed on Sunday, 9 March, just as TLAC members are beginning travel to Geneva (at which time Jonathan is unavailable to provide timely input). Thus, Bruce takes full responsibility for this VVM review version. Informal discussions on 10 March and formal presentations on 11 March about VVMs by its developers, promoters, and TTI experts are scheduled [summarized in detail in subsequent TLAC 2nd Meeting Report].

vaccines are discarded unnecessarily, such as when breaks of unknown severity occur in the cold chain. [19, 20]

The UNICEF procurement process requires that vaccines it purchases for the developing world be approved through the WHO "prequalification" review, which serves as a surrogate national regulatory authority (NRA) for countries lacking the resources or expertise to review themselves the safety and efficacy of vaccines to be marketed.

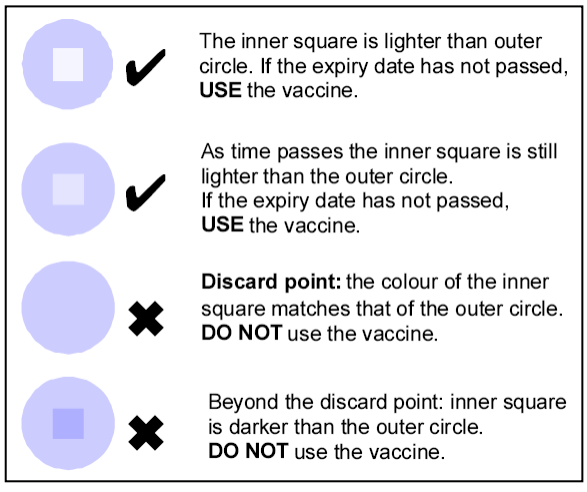
Beginning in the early 2000s, an expanding number of vaccine types beyond the original OPV were required to have VVMs. [21, 22] Upon this expansion of the VVM requirement to vaccines other than polio, vaccine manufacturers expressed various concerns about the technology and its use for their products. [9] These were discussed in a major meeting at WHO on 27 March 2002. [21] WHO published additional Q&A responses to these concerns. [22]

## *2.2 Principles of Application*

A variety of TTIs – using chemical, physical, and electronics techniques -- have been developed and used to monitor damaging heat exposures for products in different industries, particularly foods and pharmaceuticals. The landscape of TTIs – including specifically for VVMs [23]– has been reviewed extensively by Prof. Ted Labuza and colleagues at the University of Minnesota.[24, 25, 26, 27, 28, 29, 30]

VVMs are intended to show whether and when a pre-set limit of cumulative temperature exposure over time has been reached. This is indicated by a gradual change in color darkness of a special indicator ink imprinted on the label (**Figure A**). This indicator is surrounded by a circle printed with reference ink that does not change color darkness. When the darkness of the inner indicator is equal to or greater than the darkness of the outer reference ring, then the VVM is considered to have reached, so to speak, its "endpoint conversion", or to have "converted". For convenience, these terms are used in this document to describe that point. Further details on the function and field use of VVMs are in published references. [31, 32]

**Figure A. Illustration and instructions for VVM use.**


The inner square is lighter than outer circle. If the expiry date has not passed, USE the vaccine.
As time passes the inner square is still lighter than the outer circle.
If the expiry date has not passed, USE the vaccine.
Discard point: the colour of the inner square matches that of the outer circle.
DO NOT use the vaccine.
Beyond the discard point: inner square is darker than the outer circle.
DO NOT use the vaccine.

There are currently in 2009 four distinct versions of VVMs, each designed to reflect a different degradation rate in order to match better the actual thermostability of specific vaccines (**Table 1**). [33, 34] These different "models" are currently referred to as VVM2, VVM7, VVM14, and VVM30, with the number indicating the approximate number of days by which a VVM held at +37ºC would convert to indicate the accompanying vaccine vial should be discarded. Before 2004, they were referred to as the **D** ("least stable"), **C** ("moderate stability"), **B** ("medium stability"), and **A** ("high stability") versions, respectively. These letter designations were dropped in favor of the more intuitive numerical ones.

Because the OCC strategy[8] before the TLAC focuses exclusively at this time on hepatitis B vaccines (HBV), for convenience, examples and specifications discussed in this review will focus on the VVM30, which is the version applied to these relatively heat-stable vaccines.

**Table 1. VVM variants with common vaccine types using each.**

| VACCINE VIAL MONITOR TYPE | VACCINE TYPES ASSIGNED, *inter alia* |
|---|---|
| **VVM2** ("D. Least Stable") | **OPV** |
| **VVM7** ("C. Moderate Stability") | **BCG**, **DTP**, **MEA**, **MMR**, **$PNU_{cn}$** |
| **VVM14** ("B. Medium Stability") | **$DTP_W$**, **HIB**, **ROT** |
| **VVM30** ("A. High Stability") | **HBV** |

**OPV** = oral polio vaccine
**BCG** = Bacille Calmette Guérin (TB)
**DTP** = diphtheria+tetanus+pertussis
**MEA** = measles
**MMR** = measles+mumps+rubella
**$PNU_{cn}$** = pneumococcal conjugate
**$DTP_W$** = diphtheria+tetanus+pertussis(whole cell)
**HIB** = haemophilus influenzae type B
**ROT** = rotavirus
**HBV** = hepatitis B

## *2.3 Mechanism of Action*

This change in color darkness of the VVM indicator – more precisely measured mechanically as optical density (OD) – is the result of an irreversible chemical reaction based on the polymerization of substituted diacetylene monomers. [23] The OD change is irreversible, even if the VVM returns to cold temperatures. This change in OD is reported to occur within certain parameters in accordance with an Arrhenius formula, which predicts the typical rate of a chemical reaction as affected by temperature. The change in OD is intended to integrate the effect of each unit of time spent at each temperature.

As stated in reference 8:

> "The Arrhenius relationship defines the rate constant, k, of a variation with temperature:
>
> $$k = A_O \exp(-E_a/RT)$$
>
> "In this equation, $A_o$ and $E_a$ are experimentally-determined constants specific to the reaction, and R is the universal gas constant. The activation energy, $E_a$ , determines how the rate changes with temperature, T, which is expressed in degrees Kelvin.
>
> "For a VVM30, the [color] changes essentially linearly with time and reaches its end-point by 30 days at 37°C, so the rate constant equals 1/30 per day at this temperature.

> The experimentally determined activation energy of 27.1 kcal/mole is used to determine the [color] change for any other time-temperature combination or to plot an Arrhenius chart of the end-point as a function of temperature.
>
> "Similarly, the characteristics of most proteins are seen to follow Arrhenius kinetics, at least in the temperature range where they are not undergoing a physical change, such as when, for example, freezing causes an aggregation of particles, or at temperatures approaching 60ºC, when most proteins are inactivated."

### *2.4 Caveats*

The generally parallel slopes of different VVM versions shown to TLAC in shelf life plots [8] suggest they all share similar activation energies $E_a$ , but have different *k* constants in crossing the Y-axis intercepts at any given temperature.

But the times at various temperatures until a VVM indicator reaches endpoint, and the times until a vaccine loses its potency (ability to induce a desired immune response to protect from disease) may follow different Arrhenius kinetics, if at all.

According to a leading TTI expert,[35] Arrhenius reaction rates cannot be determined by observations at only two different temperatures. But the 1997, 2002, and 2006 performance specifications for VVM2 (for OPV) require only testing at +5º and +37º C, but not at the usual third +25º C temperature for VVM7, VVM14, and VVM30. WHO states by footnotes, "**VVM (Arrhenius) reaction rates determined at two temperature points*" for VVM2.

Theodore P. Labuza comments that Arrhenius plots (rate constant *k* vs. the inverse of temperature in degrees Kelvin) are rather inscrutable. More understandable, he advises, are plots of the log of time to VVM conversion (or to vaccine potency loss) versus temperature. These are called *shelf-life plots*, as illustrated in **Figure I**, far below.

Such graphs use a logarithmic *Y* axis to plot the mean days until VVM endpoints are reached and until vaccine potency is lost. The arithmetic *X* axis plots the temperature points at which observations occurred. To prove the applicability of a VVM color change to potency loss of a vaccine, both the VVM and the vaccine must be tested at a minimum of three fixed temperatures over the range of temperatures they may experience.

The closer and more parallel are the VVM and potency shelf-life plots, the more accurately would the VVM predict when a vaccine has lost potency.

Neither WHO nor the manufacturer of the HEATmarker VVM perform testing to determine the loss of potency of a vaccine over time at specific temperatures, and thereby be able to calculate its Arrhenius kinetics and plot its shelf life. Instead, WHO places the burden on vaccine manufacturers who wish to supply their products via UNICEF to themselves pick one of the four existing VVM types that best match the time-temperature degradation of its vaccine.

TLAC was not provided with any data demonstrating the relationship of the density change of the HEATmarker™ VVM to potency loss for any vaccine, as in **Figure I** for another product considered by WHO before adopting the HEATmarker™: the 3M MonitorMark™.

Another concern is that very brief but high temperature spikes may immediately denature and render impotent a biological product such as a vaccine, but not necessarily cause a current VVM to reach its endpoint because of the very short time involved. This situation was

acknowledged in a proposed TempTime patent filed in 2006 to add both heat-spike and freeze detectors to a VVM).

### 2.5 Conceptualizing Function

To explain how a VVM works when subjected to varying temperatures for varying times, consider a VVM30 with an intended limit, at a steady +37°C, of 30 days. For the sake of this discussion, this number of days may be considered 100% of its useful life. If the VVM30 is kept at +37°C, the color of the inner square will match the color of the reference circle at or around 30 days (**Figure A**).

If the VVM is kept at a cooler temperature, say +25°C, then the VVM will reach its endpoint after a much longer period (e.g., ~193 days according to specification), which is considered equivalent to the same heat damage or potency loss that would have occurred upon 30 days at +37°C.

One can continue such a thought experiment to include any number of time-temperature combinations. So, if the VVM30 is first exposed to 15 days at +37°C, then in theory it should last an additional ~96 days at a new temperature of +25°C.

One may also think of the thermostability of a VVM -- as well as that of a vaccine itself -- as a kind of bank account with an initial balance of funds when the vaccine is first filled and labeled (Stephen Zweig, personal communication, 2008). Different amounts of money will be debited from the account for each unit of time (minutes, hours, etc.) according to the temperature to which it is exposed.

For example, +2°C might result in a debit of $1 per minute, while at +8° $5 per minute might be deducted. At +15° a debit of $260 may occur, and at +45°C a whopping $9,432 could be deducted (these amounts are hypothetical and not determined by applying any Arrhenius kinetics). When the account balance reaches zero, the vaccine is no longer potent according to the predetermined specification of its manufacturer and NRA, and should be discarded.[b]

### 2.6 Affect of Light and Water

VVMs are sensitive to light, which accelerates the same polymerization reaction as does heat in increasing the OD of the indicator. Exposure to light will cause endpoint conversion earlier than otherwise would occur on the basis of its cumulative temperature exposure over time. [36] The brighter the light and the longer its exposure, the greater the effect.

According to the manufacturer, the unreacted monomer of the VVM indicator chemical is <0.1% soluble in water at room temperature and formulated in a binder that is insoluble in water.

In an independent evaluation study commissioned by WHO, of which only limited portions were provided to TLAC, the effects of water was assessed on both shade change (measured by optical densitometry) and hue/color change (by spectrophotometer). [37] Sets of VVM30-

[b] Electronic TTIs can be programmed to perform equivalent calculations for any specific thermostability profile. [56] Such devices could also immediately "close the account" were freezing to occur or a very high temperatures be experienced for more than a permissible interval.

("type A"), VVM14- ("type B"), and VVM7-imprinted ("type C") labels were submerged in a bowl of water at +5°C +/- 0.2°C for eight hours. After this period, the labels were removed from the water bath and dried carefully with absorbent paper, followed by 16 hours at +5°C in a desiccant chamber. Control labels which remained dry throughout were stored in sealed polyester pouches at the same temperatures as the soaked patches, for the same length of time, prior to exposure of all labels to +37°C for 40 days, with daily measurement of ODs.

According to page 309 of the redacted 409-page report:

> "Soaking in water seemed to decelerate the color change compared to un-soaked patches. Graphs of wet and dry OD measurements versus time of A, B and C type VVMs are included in Appendix D."

As Appendix D was not furnished to TLAC, it is unknown what effect was found upon water submersion, if any, on VVM optical-density change (in contrast to the mentioned effect on color).

## *2.7 VVM Performance Specifications*

The VVM review team was not provided with various proprietary documents on the intended function, performance, and design tradeoffs for HEATmarker™ VVMs from its development, field testing, and deployment in the 1990s.[10,12] It is presumed that VVM endpoint conversions are intended to occur a safe margin before, but reasonably close to the time the associated vaccine would lose potency. Presumably, VVM developers gave more weight to reducing impotency error at the price of somewhat more wastage error. It is also likely that necessary tradeoffs were made between precision and affordability.

VVMs by the current manufacture of the HEATmarker went into use only on vials of oral polio vaccine (OPV) in the mid-to-late 1990s.[10,12] But TLAC was not provided any records of these earliest and prior intervening performance specifications and testing.

Only three iterations of their performance specifications were available for comparison, along with associated testing procedures for validation of individual lots. These occurred in 1997 [38] (26 September), 2002[39] (25 March), and 2006 [40] (30 November).

The reasons for these changes have not been described publicly, nor informed to TLAC members. It is unknown whether the chemistry and formulation of the VVMs was modified to satisfy changed specifications, or if the specifications were revised to permit unmodified VVMs to more readily and conveniently satisfy them.

### 2.7.1 1997 Specifications

The specifications of the VVM for the oral polio vaccine (OPV) indicates it was last revised on 27 September 1997 (document WHO/EPI/LHIS/97.09, of 35 pages). [38] Its page 1 states at bottom, "*Date of last revision of this module: 1 January 1998*". On its actual pages 18-to-21 [of total 35] that are specific to the VVM for OPV is stated, "*Date of last revision: 29 September 1997*" [nominally pp. 14-17 at these pages' bottoms].

There was only one VVM type – for OPV – when this first VVM specification was published. It would later become known as the "VVM2" version. Its original specification (**Figure B**) effectively required that no more than 5% of the VVM samples should fail to reach endpoint after 48 hours at +37°C, or after a different time limit if

published by the vaccine's manufacturer. At +5°C, more than 90% of VVMs should reach endpoint beyond the labeled shelf life at that temperature of the particular manufacturer's vaccine. Also, no more than 5% of the labels should reach endpoint more than 25% earlier than these target times – 36 hours at +37°C – but indeterminable at +5°C without knowing a specific vaccine's shelf life.

In the **Figure B** below, the two "12.5%" notations appear to reflect the definition of the premature VVM conversion window to be 25% earlier (@36 hours) than the target timepoint for expected conversion (@48 hours). Within this window between 36 hours and 48 hours after testing begins, at least 90% of endpoint conversions should occur.

**Figure B. Portion of the original 1997 performance specification[39] (p. 20 of 35) for VVMs. The OPV version was the only one at that time.**

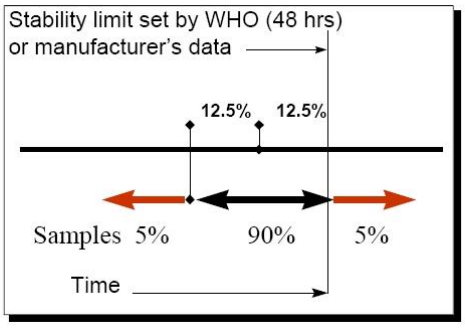
**VVM reaction rates: (See Figure below)**

4.1 At +37°C and RH 25-35% and RH 55-65%, at least 90% of VVMs tested should reach the end point within a range of time whose upper limit is the WHO stability standard for oral polio vaccine (37°C for 48 hours) or a period set by the vaccine manufacturer, based on published vaccine stability data, and whose lower limit is 25% below the upper limit.

4.2 At +5°C ± 3°C and RH 25-35% and RH 55-65%, at least 90% of VVMs tested should reach the end point within a range of time whose upper limit is the vaccine manufacturer's shelf life of the vaccine at +5°C ± 3°C and whose lower limit is 25% below the upper limit.

4.3 A tolerance is allowed in the above tests for up to 5% of VVM samples tested to reach the end point after the upper limit and 5% before the lower limit.

4.4 The colour change shall be linear in its response to cumulative heat exposure within the limits of the allowed variation. The observer shall be able to distinguish between unchanged, 50% and the end point of the indicator.




Four principal tests are set forth in the 1997 iteration to assess compliance with these specifications (actual pages 32-35 [nominal numbering at bottom 28-31]). The first, **Test 1**, performed at +37°C, at relative humidity (RH) ~30%, and in the dark, is shown in **Figure C**. The other tests are similar and vary only in parameters (**2:** +37°C / ~60%RH / no light; **3:** +37°C / RH ~30% / indirect light, and **4:** +8°C / ~30%RH / no light).

**Figure C. Test 1 of procedures to determine compliance with the 1997 performance specification.** [38]

**VVM reaction rate; +37ºC, 25-35% RH, no light, Test 1**

Sample set 'A' (60 samples) should be exposed to 37°C +/- 0.2°C. After 75% of the agreed test period in the cabinet without light and with a relative humidity of 30 % +- 5% the first portion (20 VVMs) of the sample set 'A' should be removed from the cabinet. The active surface on all 20 VVM samples should be read, using a colour densitometer and recorded.

The second portion (20 VVMs) of the sample set should be removed from the cabinet after 100% of the agreed test period. The readings and recordings should then be repeated.

The third portion (20 VVMs) of the sample set should be removed from the cabinet after 125% of the agreed test period. The readings and recordings should then be repeated.

### 2.7.2 2002 Specifications

The revised specifications issued in 2002 [39]were the first to include the additional 3 types VVM7, VVM14, and VVM30 not included in the initial 1997 specification for OPV alone (VVM2).

In addition to adding three more VVM types, another substantive difference in the 2002 specifications from the 1997 one was elimination of the requirement for real-time assessment of endpoint conversion at the +5°C temperature (**Figure E**). This was now determinable by extrapolation from data at the remaining two temperatures, 25º and 37ºC. No details are provided on the rationale, assumptions, and methods for such extrapolations.

In the revised 2002 version [39] there is no requirement for testing after exposure to [direct] light nor indirect light, as in the prior 1997 version. [38]

Another substantive change was to relax the 1997 specifications by shortening the window after test start for premature endpoint conversions that could fail the test specifications at +25° C (and at 5º C by extrapolation).

This is illustrated by the two "20%" entries in **Figure D**, and the "40% below the upper limit" described in **Figure E**. Thus, for a VVM30, at +25°C, the early cutoff by which no more than 5% of VVMs may convert prematurely would be 115 days after test start (40% below 193 days), compared to 145 days after test start in the 1997 specifications.

**Figure D. Explanatory cartoon of the 2002 Performance specifications for VVMs.** [39]

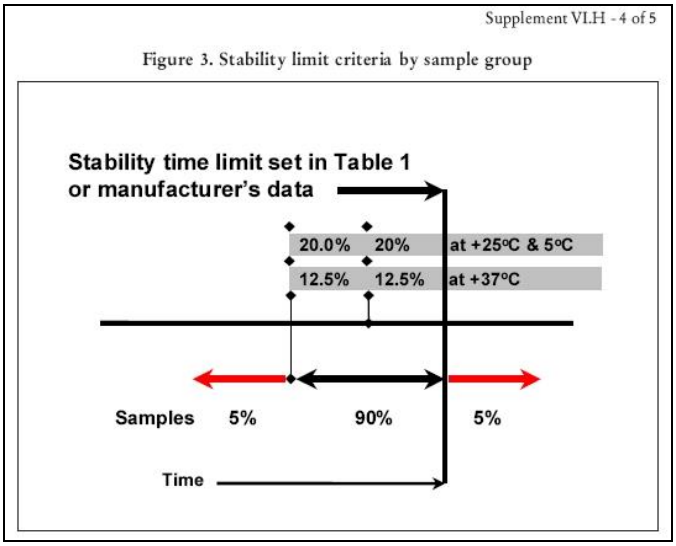



**Figure E. 2002 VVM performance specifications** [39] **with key changes from 1997 highlighted in yellow.**

Table 1: VVM reaction rates by category of heat stability

| Category: (vaccines) | No. days to end point at +37°C | No. days to end point at +25°C | Time to end point at +5°C |
|---|---|---|---|
| VVM30 High stability | 30 | 193 | > 4 years |
| VVM14 Medium stability | 14 | 90 | > 3 years |
| VVM7 Moderate stability | 7 | 45 | > 2 years |
| VVM2 Least stable | 2 | NA* | 225 days |

* *VVM (Arrhenius) reaction rates determined at two temperature points*

At +37°C, RH 33% +/-5% and RH 75% +/-5%, at least 90% of VVMs tested should reach the end point within a range of time whose upper limit is shown in Table 1 or a period set by the vaccine manufacturer, based on published vaccine stability data, and whose lower limit is 25% below the upper limit (see Figure 3).

At +25°C (ambient humidity in submerged plastic/foil pouch) at least 90% of VVMs tested should reach the end point within a range of time whose upper limit is shown in Table 1 for VVM30, VVM14 and VVM7 categories, or a period set by the vaccine manufacturer, based on published vaccine stability data, and whose lower limit is 40% below the upper limit (see Figure 3).

At 5°C (ambient humidity in submerged plastic/foil pouch), all VVM30, VVM14, and VVM7 samples should reach the end point after the lower time limit specified in Table 1. Conformance can be determined by extrapolation from high temperature (25 and 37°C) data. At 5°C (ambient humidity in submerged plastic/foil pouch), at least 90% of VVM2 samples tested should reach the end point within a range of time whose upper limit is 225 days and whose lower limit is 40% below the upper limit (see Figure 3).

A tolerance is allowed in the above tests for up to 5% of VVM samples tested to reach the end point after the upper limit and 5% before the lower limit (see Figure 3).

The colour change shall be monotonic in its response to cumulative heat exposure within the limits of the allowed variation. The observer shall be able to distinguish between unchanged, 50% and the end point of the indicator.

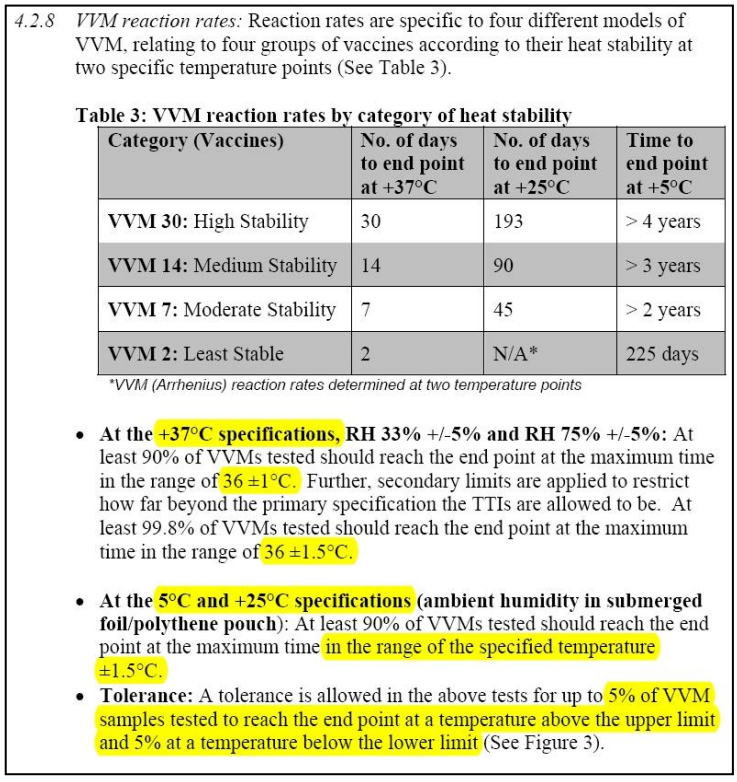
No rationale is provided for changes in the 2002 VVM specifications from the prior 1997 ones. Was the chemistry and formulation of the VVM changed that required new specifications? Or did the product remain the same, but specifications modified to more easily pass them?

### 2.7.3 2006 Specifications

The most significant and dramatic changes to the VVM specifications were formally promulgated on 30 November 2006 in its current specifications document [40] and associated test protocols. [41]

They widened the tolerable precision of the temperatures at which testing should occur (**Figure F**), adding a separate 99.8% required range in near-incomprehensible terms that challenge intuitive comprehension and interpretation (**Figure G**), [acknowledged even by its manufacturer's representative (pp. 8-10 of 30)].

**Figure F. Current 2006 VVM performance specifications, showing temperature range changes from 2002 highlighted in yellow. [40]**



4.2.8 *VVM reaction rates:* Reaction rates are specific to four different models of VVM, relating to four groups of vaccines according to their heat stability at two specific temperature points (See Table 3).

**Table 3: VVM reaction rates by category of heat stability**

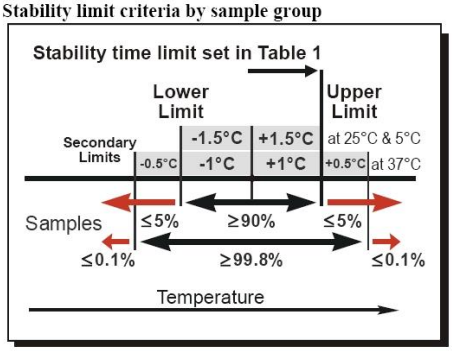
| Category (Vaccines) | No. of days to end point at +37°C | No. of days to end point at +25°C | Time to end point at +5°C |
|---|---|---|---|
| **VVM 30:** High Stability | 30 | 193 | > 4 years |
| **VVM 14:** Medium Stability | 14 | 90 | > 3 years |
| **VVM 7:** Moderate Stability | 7 | 45 | > 2 years |
| **VVM 2:** Least Stable | 2 | N/A* | 225 days |

**VVM (Arrhenius) reaction rates determined at two temperature points*

- **At the +37°C specifications, RH 33% +/-5% and RH 75% +/-5%:** At least 90% of VVMs tested should reach the end point at the maximum time in the range of 36 ±1°C. Further, secondary limits are applied to restrict how far beyond the primary specification the TTIs are allowed to be. At least 99.8% of VVMs tested should reach the end point at the maximum time in the range of 36 ±1.5°C.
- **At the 5°C and +25°C specifications (ambient humidity in submerged foil/polythene pouch**): At least 90% of VVMs tested should reach the end point at the maximum time in the range of the specified temperature ±1.5°C.
- **Tolerance:** A tolerance is allowed in the above tests for up to 5% of VVM samples tested to reach the end point at a temperature above the upper limit and 5% at a temperature below the lower limit (See Figure 3).

**Figure G. Current 2006 VVM performance specifications, with significant methodological changes from 2002 highlighted in yellow.** [40]

**Figure 3. Stability limit criteria by sample group**




- **Allowable range of end points:** Table 4 defines the allowable range of end points such that 90% of a production lot must reach the end point at the specified time within a range of ±1°C and that 99.8% of the lot must reach end point within a range of ±1.5°C.

**Table 4: Allowable range of end points**

| VVM Type | Primary Limits: ±1°C measured at upper limit (including OD tolerance) | | Secondary Limits: ±1.5°C measured at upper limit (including OD tolerance) | |
|---|---|---|---|---|
| | Lower Limit | Upper Limit | Lower Limit AQL=0.1% | Upper Limit AQL=0.1% |
| VVM30 | -0.19 | 0.03 | -0.24 | 0.06 |
| VVM14 | -0.15 | 0.03 | -0.18 | 0.06 |
| VVM7 | -0.11 | 0.03 | -0.13 | 0.05 |
| VVM2 | -0.09 | 0.03 | -0.10 | 0.04 |

## *2.8 Price, Cost, and Economic Analysis*

In the mid-1990s, the original target price desired in the WHO specification for the development of VVMs was US 5.2¢ (US$0.052) per label. [42] In 2001 and 2002, pricing from 3.3¢ to 5.05¢ was reported on page 27 of reference 22. In 2006, an official of the Temptime Corporation, the sole manufacturer of VVMs, wrote in a Technet posting that:

> "A vaccine supplier purchasing a standard Full Label VVM or standard Dot VVM in 2006 for vaccine to be sold solely for use in the donor market can expect a price range of between 3.3 US cents (VVM Dot) to 5.6 US cents (Full Label). Prices vary based upon VVM category, full label size and order quantity. A copy of the Price Guides is available to vaccine manufacturers upon request …"

The Temptime 2008 World-Wide Pricing Guide indicated prices ranging from U.S. 4.05¢ to 6.42¢, depending on VVM model (dot vs. full label) and order size. [43] The price range was slightly lower for the 2007-2009 UNICEF tender, ranging from U.S. 3.39¢ to 6.36¢. [44] Price increases slightly as the VVM type progresses from VVM2 to VVM7 to VVM14 to VVM30. These are base prices without various printing and delivery options.

An industry source recently suggested a current price range to them of around U.S. 6¢ to 9¢ per label. Another was more definitive in reporting its price around U.S. 8¢, compared to their usual cost for a plain label of about U.S. 1¢ to 1.5¢. These prices are reported to be highly concessional for the developing world.

VVM labels purchased by vaccine manufacturers must be preprinted by Temptime with any needed text, logos, symbols, barcodes and other printing content required on the label by the

vaccine manufacturer. One informant indicated that the Temptime machines for such general printing were somewhat dated and could not handle special colors, smaller font sizes, and other features of modern label printers.

The overall cost of VVMs might roughly be estimated by multiplying the total number of doses of vaccine procured by UNICEF in 2007 – 3.2 billion [45] – by a likely range of U.S. 4¢ to 8¢ per label, and then dividing by the common 10-doses-per-vial packaging.

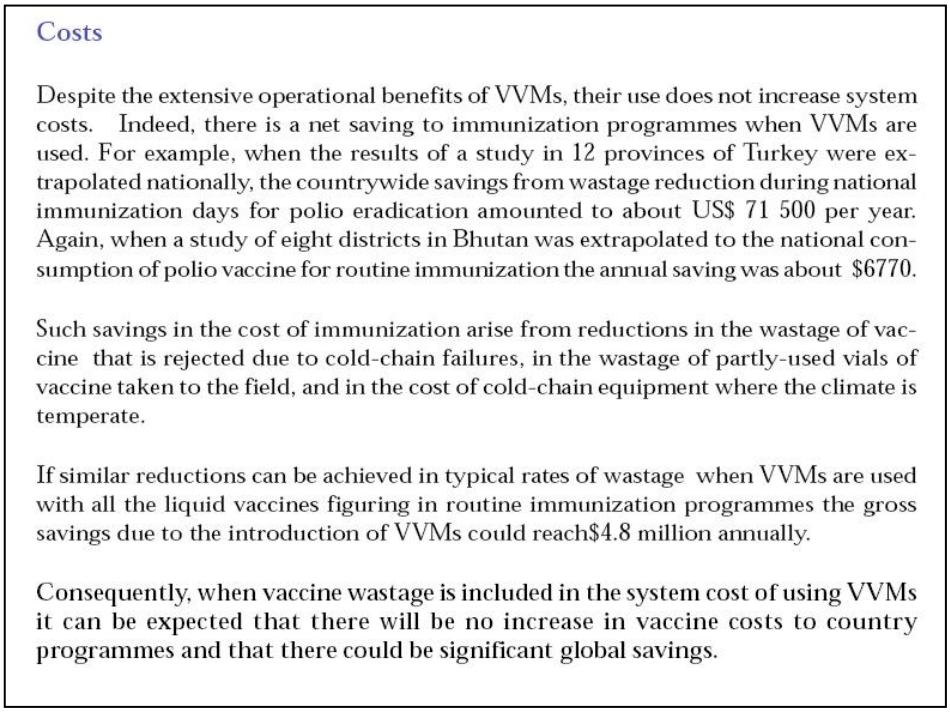
This produces a total annual global cost estimate for VVMs from U.S. $12.8 million to $25.6 million (less the baseline cost of conventional labels). This amount compares to the total U.S. $617 million value of all vaccines that UNICEF reported it procured in 2007.[45]

This is a conservative cost estimate which ignores the relatively small numbers of vials with fewer than 10 doses. As new vaccines and their smaller-dose and even single-dose vaccine vials are procured, the absolute and relative costs of VVMs to immunization donors and other vaccine purchasers will increase.

The modern era of immunization policymaking and philanthropy has been greatly influenced by economic analyses. This review has been unable to find, nor been furnished with, any rigorous cost-benefit, cost-effectiveness, or related quantitative modeling or empirical research on the use of VVMs in the global EPI system.

A joint WHO-UNICEF statement published in 1999 stated that use of VVMs "*does not increase* [immunization] *system costs*" (**Figure H**). [19]

**Figure H. Claimed net savings to immunization programs from VVMs. [19]**



Costs

Despite the extensive operational benefits of VVMs, their use does not increase system costs. Indeed, there is a net saving to immunization programmes when VVMs are used. For example, when the results of a study in 12 provinces of Turkey were extrapolated nationally, the countrywide savings from wastage reduction during national immunization days for polio eradication amounted to about US$ 71 500 per year. Again, when a study of eight districts in Bhutan was extrapolated to the national consumption of polio vaccine for routine immunization the annual saving was about $6770.

Such savings in the cost of immunization arise from reductions in the wastage of vaccine that is rejected due to cold-chain failures, in the wastage of partly-used vials of vaccine taken to the field, and in the cost of cold-chain equipment where the climate is temperate.

If similar reductions can be achieved in typical rates of wastage when VVMs are used with all the liquid vaccines figuring in routine immunization programmes the gross savings due to the introduction of VVMs could reach$4.8 million annually.

Consequently, when vaccine wastage is included in the system cost of using VVMs it can be expected that there will be no increase in vaccine costs to country programmes and that there could be significant global savings.

The 1999 statement claimed major cost savings from VVM use in a mass polio campaign in Turkey and in routine immunization in Bhutan. Neither the reports from Turkey [46] (described in § **3.2**) and from Bhutan [c] would seem to justify such generalized conclusions.

### *2.9 Implementation and Applications*

#### 2.9.1 Batch testing

It is not clear whether vaccine manufacturers are required to conduct performance assays on the VVM labels they purchase. Documents provided to TLAC by Temptime [36] describe assessments of endpoint OD conversion measurements on +37°C-incubated VVM30s to be performed at 75% (22.5 days), 100% (30 days), and 125% (37.5 days) of the target date at that temperature. At +25°C, the ODs would be assessed at 60% (116 days), 100% (193 days), and 140% (270 days) of their nominal longevity.

On the other hand, one vaccine manufacturer informant indicated that this or similar testing is not expected of them, but rather by the VVM manufacturer. When VVM labels arrive, they are simply stored deep frozen to arrest their degradation until the actual date of application to the filled vaccine vials.

#### 2.9.2 Cold Chain

General background on the use and assessment of the cold chain in immunization programs is available elsewhere. [47, 48, 49] The use of a "fast chain" that relies on VVMs to reduce dependence on cold chain equipment for more flexible management of OPV campaigns has been described. [50]

## 3. Examining the Evidence for VVMs

### *3.1 Performance*

From a regulatory perspective, a VVM is a medical device somewhat analogous to a diagnostic test. Instead of predicting the presence of a disease or condition, of course, the VVM is intended to indicate when a vaccine has lost potency below an arbitrary level set by its manufacturer and regulatory authority, such that it may not effectively immunize the recipient.

In assessing new diagnostic tests, they are usually compared to the best available but often tedious and expensive existing test for a disease or condition – often referred to as the "gold standard". Error rates for the new test are often quantified in terms of *false positivity*, *false negativity* and *predictive values positive* and *negative* (influenced by disease incidence)

These concepts can be applied to VVMs, despite their different purpose. In this review, two new terms are used to replace false positivity and false negativity as measures of error. The former is termed herein "*wastage error*", and the latter "*impotency error*". *Wastage error* reflects when a VVM reaches its endpoint conversion and the vial is discarded before its

[c] PATH. Vaccine Vial Monitor Impact Study Results - Kingdom of Bhutan - July 1997 through November 1998. 30 November 1999.

associated vaccine has actually lost its potency. Theoretically, in such cases, still usable vaccine is discarded.

*Impotency error* represents the opposite situation when the vaccine has lost its potency through exposure to heat, but the VVM has not yet reached its endpoint to indicate that it should be discarded. In such cases, recipients of that vaccine may not be protected from disease, with subsequent risks to their health and to their community.

These two types of error vary inversely to each other and thus illustrate tradeoffs in designing and setting the target time for endpoint conversion. As the endpoint is moved to an earlier point in time, wastage goes up and impotency down. Conversely, delaying the endpoint decreases wastage error but increases impotency error.

There are four main aspects on which the performance of VVMs may be evaluated in order to estimate their *wastage* and *impotency* errors, and the resulting consequences, both financial and human:

1. How closely do VVMs satisfy their specifications to convert around a certain target day when held at their key "sentinel" temperatures?
2. How well do VVMs match the actual stability of the vaccines on which they are applied? [51]
3. How accurately can health workers compare the VVM indicator's optical density to its reference ring when the VVM is near or at its endpoint conversion?
4. What is the actual frequency in which vaccines are discarded in ongoing immunization programs due to VVM conversion before use?

These areas are discussed in the following subsections.

### 3.1.1 Assessing Performance to Specifications

This review exercise by TLAC could not find, nor was provided, any report of original data from actual bench studies on VVM production batches in accordance with VVM specifications, nor summaries over time of the rates of satisfied and failed testing for same.

Only summaries from other documents, or limited pages insufficient to determine or interpret methods and results, were provided for requested reports by independent laboratories commissioned by WHO to study VVMs, [37, 52, , 53] as mentioned in references 10 and 51.

Of primary value would be a straightforward, intuitive, pivotal assessment of the actual days at which VVMs reach endpoint conversion when maintained at each of their key sentinel temperatures (+5°C, +25°C, and +37°C). Measurements at only two temperatures cannot determine Arrhenius kinetics. [35]

Such data would permit determination of point estimates (mean, median), measures of dispersion around them (standard deviations, confidence limits), and serve as a pillar for "bridging" with simpler and shorter lot-release assays using potential surrogates like OD dispersion measured at a single time point (see § **2.7.3**).

One brief data summary was provided to TLAC by the VVM manufacturer on 1 March 2009, [54] describing studies of six lots of VVM30s of differing ages from 2000 to 2002. Twenty samples from each lot were examined at either 22.5, 30, or 37 days for endpoint conversion at +37°C. A similar 20 per lot were examined at 116, 193, and 270 days at +25°C. In these samples from six lots, no VVMs were found to have converted before the early time, and all were found to have converted by both the middle (target) time and the post-target time. The study design did not permit determination of mean days until conversion and confidence limits around such point estimates.

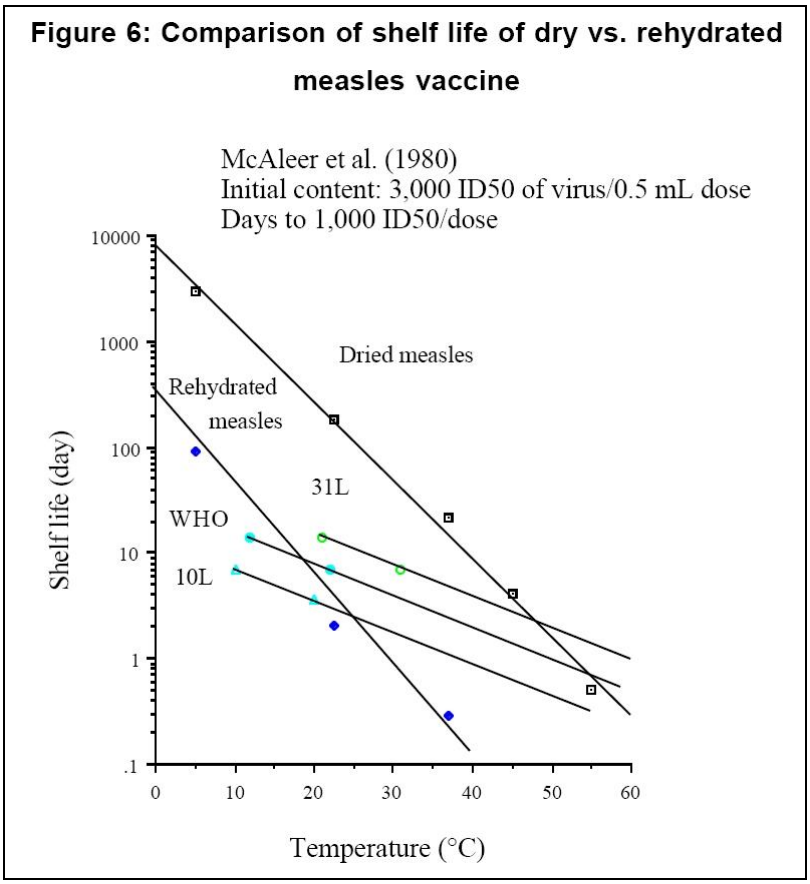
### 3.1.2 Assessing VVM Matching to Vaccine Stability

The next critical area for assessment of VVMs is how well the VVM performance matches the actual stability of the vaccine to which it is applied. This is most intuitively illustrated and understood by simply graphing the mean time until endpoint or loss of potency for both the VVM and the associated vaccine, as in **Figure I** (this graph does not show a Temptime VVM, but three 3M TTI products).

As illustrated in **Figure I**, for a given temperature, when the vaccine line or curve ("Dried measles", "Rehydrated measles") is higher than the TTI curve (31L, WHO, 10L), the vertical distance between the two lines represents potential premature conversion of the TTI and thus a source of *wastage error*.

When the vaccine line/curve lies below the TTI line/curve, as in the extrapolations of the TTI lines at extremely high temperatures, the vertical distance between them reflects potential delayed conversion, and thus *impotency error*.

**Figure I. From Labuza & Fu. [23] (citing McAleer, et al) [55] Comparison shelf life plots of the stability of lyophilized and reconstituted measles vaccine with three prototype MonitorMark™ time-temperature indicators (TTIs) developed for vaccine vials by the 3M Corporation. Data point series "31L", "WHO", and "10L" represent the mean days until endpoint conversion at indicated temperatures of each prototype. 3M subsequently abandoned further adaptation of MonitorMark for the vaccine market.**




The different slopes between the three 3M TTIs and the vaccines in this figure suggests that they have quite different activation energy constants in their equations and thus do not follow the same Arrhenius kinetics. TLAC has not been furnished any comparable graphs to illustrate how current HEATmarker VVMs (TTIs) match their associated vaccines.

As commented earlier (§ **2.4**), WHO requires manufacturers who wish to furnish the UNICEF-procured vaccines to purchase and affix an available VVM that in the company's sole opinion best matches the potency degradation of their vaccines. However, none of the available VVMs may be a good match. Since the most "heat-stable" of the HEATmarkers are designated as the VVM30, significant wastage error can occur for vaccines that may have substantially greater longevity, such as some hepatitis B products.

In not-for-attribution discussions with vaccine industry officials from multiple companies, the primary complaint was that VVMs do not reflect the actual [higher] stabilities of some of their vaccines, particularly at some temperatures. The primacy of

this "stability mismatch" complaint has changed little from among those concerns expressed by vaccine manufacturers at the 2002 forum with WHO. [9,21,22]

For example, one manufacturer reported a product requiring a VVM2 because of its loss of longevity of potency at +37°C, but at +5°C it retains potency for 3 or more years, and is approved by its regulatory authority with a shelf life after filling of 3 years (~1,096 days). However, as VVM2s are designed at typical storage temperature of +5°C to convert and "expire" at 225 days, this would result in significant wastage when properly-stored and still-potent vaccines are discarded more than 2 years before product expiration. Clearly, the Arrhenius kinetics for potency loss by the vaccine is significantly different from and mismatched with its attached VVM.

This mismatch for some hepatitis B vaccines (HBV) at +37°C and the VVM30s is illustrated in tables from WHO publications 33 (**Figure K**) [33] and 34 (**Figure J**).[,34] Stabilities at +37°C from 2 to 7 months are reported for some unidentified HBV products, substantially longer than the VVM30 would convert.

**Figure J. Summary of stability of HBV from various manufacturers, from 1998 reference 33.** [33]

Table 3: Stability of five hepatitis B vaccines as indicated by immunogenicity tests on animals

| Vaccine tested | Parameters used in testing vaccines | Storage temperature (°C) | | | |
|---|---|---|---|---|---|
| | | 2 - 8 | 20 - 26 | 36 - 40 | 45 |
| A (plasma) | Longest storage without significant loss of potency | 24 months | 12 months | 3 months | - |
| C (plasma) | Remaining potency (%) after specified time | 100% after 24 | 70% after 24 | 70% after 24 | - |
| D (plasma) | Longest storage with relative potency upper confidence interval >1 | 44 months | - | - | - |
| E (recombinant) | Longest storage with relative potency upper confidence interval >1 | 53 months | 12 months | 7 months | 1 month |
| | Half life* | - | 9 months | 1 month | 3 days |
| F (plasma) | Half life | >3 years | 4 months | 7 days | - |

* Half life: time at which 50% loss of original potency occurs

*Source: Manufacturers' data.*

**Figure K. Summary of stability of HBV from various manufacturers, from 2006 reference 34.**

Table 5: Stability of hepatitis B vaccines as indicated by immunogenicity tests

| Manufacturer (Mfr) | Temperature °C | | | | Reference |
|---|---|---|---|---|---|
| | 2-8 | 20-26 | 37 | 45 | |
| Several Mfrs | 4 years | 1 year | 2-6 months | 1 week | (*87*), Mfr data |
| A | - | - | 3 months | - | Mfr data, In vitro potency |
| B | - | 6 months | 1 month | - | Mfr data |
| C | - | - | 1 month | 1 week | (*140*), human data |
| D | - | 30 days | 1 week | 3 days | Mfr data |

### 3.1.3 Assessing Accuracy of User Readability

Another potential source of *wastage error* and *impotency error* in day-to-day field use of VVMs is the degree of accuracy by which human beings actually can read and interpret correctly the VVM. Unlike densitometers used in bench assessments, human vision may have trouble distinguishing the darkness of the central indicator square and the reference ring of the VVM (**Figure A**) when the VVM is approaching endpoint.

The 1997, 2002, and 2006 VVM performance specifications included a lax "*Observer perception test*" to assess the abilities of "untrained observers" in a test facility to read VVMs. For example, from the 2006 VVM specifications: [41]

> *5.2.15 Test 11: Observer perception test: (applies to all VVM categories)*
>
> - **Step 1:** Attach 15 VVM samples to empty 2 ml vials. Five of the VVM samples should be at the start point, five should be conditioned to 50% of the colour change to end point and five should be at the end point.
> - **Step 2:** Place the samples in a box in a random order and store in a freezer below -24°C to prevent further colour change.
> - **Step 3 – evaluation:** Five untrained observers, working independently under tungsten or fluorescent light at 100 lux on the working plane, are to sort the vaccine vials into three groups (unchanged, 50% changed, and end point). Record the level of the light used.
> - **Acceptance criterion:** All five observers are able to sort the three groups of vials with 100% accuracy.

A more realistic assessment would assess the accuracy of human perception in both a test facility and in field use when the OD of the indicator inner square approaches and even exceeds the OD of the reference outer circle. Presumably, such studies were performed in the development of VVMs, but they have not been published in the biomedical literature or been shared with TLAC.

This VVM review by TLAC, however, examined pre-market user accuracy test data from the AvoSure™ PT PRO+ diagnostic medical product sold in the U.S. market. This product utilized the same type of TTI from the corporate predecessor manufacturer of the

HEATmarker™ for VVMs (although not necessarily sharing the same chemical formulation) (**Figure L**). [56,d]

The AvoSure™ PT PRO+ and related products (Avocet Medical, Inc.) are kits containing very heat-sensitive reagents for consumer use outside of certified laboratories to monitor the effect of anticoagulant therapy on prothrombin clotting time.

**Figure L. VVM-like TTI manufactured by Lifelines Technology, Inc. (corporate predecessor of VVM manufacturer, Temptime Corporation) applied to a box of heat-labile reagents for the AvoSure™ PT PRO+ (Avocet Medical Inc.) prothrombin time test kit for home monitoring of anticoagulant therapy.**

Verify that the test strips have been stored properly. If the temperature indicator has changed color and matches the last example on the guide below, Do Not Use.
TEMPERATURE MONITOR GUIDE
Inner circle is lighter than outer ring. OK to Use.
Over time, inner circle remains lighter than outer circle. OK to Use.
Inner circle matches or is darker than the color of the outer ring. Do Not Use.
AvoSure™ PT PRO+
30 Prothrombin Time Test Strips
For use with the Avocet AvoSure PT PRO+ System for the monitoring of oral anticoagulation therapy.
For health care professional in vitro diagnostic use only.
Cal Code
Capillary (CAP-bd) 12
Venous Citrated Whole Blood (CIT-bd) .... 25
Plasma / Plasma Proficiency (Plas) ..... 13

In a pre-licensure study of user accuracy, the Avocet company used a densitometer to determine the actual indicator ODs of 12 HEATmarkers fixed at various stages from 0.35 OD units (well-before expiration) to 0.50 (beyond expiration). The reference rings averaged 0.46 OD units. A sample of 30 employees – 15 female and 15 male – were asked to judge whether or not the 12 indicators had expired. Each was provided with a strip carton with the Temperature Monitor Guide on its side (**Figure L**) to use as reference.

d Stephen Zweig, personal communication, 2008. According to the kit developer, review of this product by the U.S. Food and Drug Administration (FDA) included careful scrutiny of how well the endpoint conversion of the HEATmarker™ matched the stability of the reagent. The FDA was said to want data assuring that the TTIs were tuned to convert to endpoint shortly before the reagent lost potency. The consequence of using impotent test strips could be false results and serious bleeding events.

The results in **Figure M** reveal false-positive rates of *wastage error* (above the red line) by 7% to 33% of participants judged that the fixed ODs indicated ***not*** to use the product, when indeed it was still OK by densitometer measurement. The false negative rates (corollary of *impotency error)* (below the red line) ranged from 17% to 47%, depending on how far the central indicator color had darkened equal to or beyond the endpoint OD.

To TLAC's knowledge, no such study was ever performed using health workers in the field using EPI vaccines with VVMs.

**Figure M. User accuracy assessment in reading Lifelines/Temptime VVM-like TTI applied to diagnostic assay for U.S. market developed by Avocet. Above the red line are the 7 TTIs whose inner indicator has not yet reached endpoint conversion according to densitometer measurements. Below the red line are the 5 TTIs which have already reached endpoint conversion because ODs of the inner indicator circle are greater than or equal to the OD of the outer reference circle.**

When does the human eye detect expiration of Lifeline time-temperature indicators?

| Inner circle Mean densitometer reading | Outer Circle Mean densitometer reading | Densitometer OK to use? | Avocet Personnel OK to use? |
|---|---|---|---|
| 0.35 | 0.46 | yes | 100% |
| 0.40 | 0.46 | yes | 100% |
| 0.41 | 0.46 | yes | 93% |
| 0.42 | 0.46 | yes | 90% |
| 0.43 | 0.46 | yes | 93% |
| 0.44 | 0.46 | yes | 73% |
| 0.45 | 0.46 | yes | 67% |
| 0.46 | 0.46 | no | 47% |
| 0.47 | 0.46 | no | 37% |
| 0.48 | 0.46 | no | 23% |
| 0.49 | 0.46 | no | 27% |
| 0.50 | 0.46 | no | 17% |

## *3.2 Experience from the Field*

Up to 2009, over a decade has passed since the gradual introduction and now universal use of VVMs procured by UNICEF for the Expanded Programme on Immunization (EPI).

In 1997, WHO published a study of comparing OPV wastage between two consecutive rounds of national immunization days in 34 health centers in 12 volunteering provinces of Turkey. [46] During the first round, by national rule, all opened OPV vials were discarded at the end of each day, as were all unopened vials if they had been taken into "outreach" away from the health center. (Contemporaneous WHO policy on handling opened vials would have permitted continued use the next day. [57])

During the second round, all opened and unopened vials continued to be used on subsequent days if their VVMs did not indicate endpoint. Accordingly, the number of discarded unopened vials, and the number of remaining doses discarded in opened vials decreased substantially in the second round.

By the time of this review, TLAC could not find similar before/after or other controlled studies in either mass campaigns or routine immunization programs performed around the time of VVM introduction to assess reductions in the frequency of discarding non-VVM-containing vaccine vials because of cold chain lapses or local policies.

TLAC also could not find objective, quantitative data from "post-marketing surveillance" of other relevant data: the frequencies by which health workers are discovering converted VVMs and properly disposing of presumed impotent vaccine before it is administered.

Whether derived from records of wasted vaccine returned or reported discarded in countries or in special immunization campaigns routinely collecting such data, or from *ad hoc* prospective studies in sentinel health centers, districts, or provinces, such quantitative surveillance data on the prevalence or incidence of VVM conversions would be useful to perform the rigorous economic analyses discussed in § **2.8** above.

## 4. Questions, Clarification, and Further Documentation

1. What is the current lot release assay methodology for VVMs? Who is responsible for performing it? What quality control or testing responsibilities for VVMs, if any, do vaccine manufacturers have upon receipt of labels?
2. What were the reasons for the changes from the 1997 specifications in 2002 and from then to 2006? Was the chemistry or formulation of any VVMs changed between these different specifications?
3. What is the derivation and meaning of the "vvm score" used to label the Y axis of Figures 1 and 2 in the Sharepoint version of reference no. 51? What are the confidence limits around the mean "vvm scores" plotted?
4. Are the kinetics zero order or first order for the change over time in OD of the VVM when assayed at fixed temperatures?
5. Please provide TLAC copies of the following documents mentioned in references 9 or 10:
    i. 1992 "Independent laboratory evaluation of LifeLines HEATmarker VVMs for OPV completed by Strasburger and Siegel laboratory"
    ii. 1992 Zimbabwe study completed by PATH and the national Ministry of Health on the impact of VVMs on measles vaccine discard rates due to heat exposure.
    iii. 1996 or later documentation or correspondence from PAHO/WHO Regional Office for the Americas explaining its non-participation in purchasing OPV and other vaccines with VVMs.
    iv. 1997 "VVM impact studies completed by WHO during NIDs in Kenya, Nepal, Tanzania and Turkey" [if not already in hand as reference 46].
    v. 2002 "Impact study conducted in Vietnam by MOH and WHO with VVMs on measles vaccine"

## 5. Documentation Awaited from Previous Requests to WHO

1. Wood DJ. Report of a study of Vaccine Vial Monitors and oral poliovirus vaccine potency. Unpublished document WHO/TECHNET.98/BK.15, 1998 (reference no. 52).

2. Full copy of the report of the Consumer Association Research and Testing Centre (UK) of its 1998-2000 conformity tests/validation of the HEATmarker™ VVM2 samples, under WHO contract, as mentioned on page 164 of reference 9 and page 2 of reference 10.

3. Full copy with annexes of the 2000-2001 Precision Measurements and Instruments Corporation (US) (PMIC) conformity tests/validation of HEATmarker™ VVM types VVM7, VVM14, and VVM30 under a WHO contract, as mentioned in references 9 and 10.

## 6. References

NOTE: Some URL hotlinks in the citations below are to documents stored at a private SharePoint accessible only to TLAC members and authorized WHO staff.


[1] International Aids Vaccine Initiative. WHO's Key Normative Processes and Institutions for Vaccines: A Primer. Policy Brief #15, April 2008 (https://www.iavi.org/media-center/publications/file/86-who-s-key-normative-processes-and-institutions-for-vaccines-a-primer). At Web Archive: click here

[2] WHO. Strategic Advisory Group of Experts (SAGE) on Immunization (www.who.int/immunization/sage/en/index.html). At Web Archive: click here

[3] WHO. WHO Expert Committee on Biological Standardization (www.who.int/biologicals/expert_committee/en/). At Web Archive: click here

[4] WHO. Global Advisory Committee on Vaccine Safety (GACVS) (www.who.int/vaccine_safety/committee/en/). At Web Archive: click here

[5] WHO. Report of the independent review team examining the advisory committees of the WHO Department of. Immunization, Vaccines and Biologicals. January 2007 (www.who.int/entity/immunization/sage/IVB_AC_Review_Final_Report.pdf). At Web Archive: click here

[6] WHO. TLAC Orientation Guide. September 2008 (TLAC-OrientationGuide-2008-optimized.pdf). At Web Archive: click here

[7] WHO Technologies & Logistics Advisory Committee (TLAC). Meeting report and recommendations, 3-4 September 2008 (http://www.who.int/immunization_delivery/TLAC-report_2008-09.pdf). At Web Archive: click here

[8] Milstien J. Out of the Cold Chain: Considerations for Hepatitis B Vaccine, Final Draft 3.0, 28 August 2008 (Milstien-OCC-Considerations-HBV-Final-2008Aug28.pdf41). At Web Archive: click here

[9] Frost LJ, Reich MR. Vaccine Vial Monitors [Chapter 7]. In: Frost LJ, Reich MR, Access: How do good health technologies get to poor people in poor countries? Harvard Center for Population and Development Studies, 2008, pp. 141-166 (http://apps.who.int/medicinedocs/documents/s18776en/s18776en.pdf) At: Web Archive: click here

[10] PATH. VVM history and milestones. September 2002 (www.who.int/entity/immunization_standards/vaccine_quality/VVM_history_milestones.pdf). At Web Archive: click here

[11] PATH. Product Introduction Case Profile: Vaccine Vial Monitors: Small Labels With an Immense Impact. February 2007 (www.path.org/files/TS_vvm_case_study.pdf). At Web Archive: click here

[12] PATH. HealthTech Historical Profile: Vaccine Vial Monitors. June 2005 (www.path.org/files/TS_htiv_vvms.pdf). 2006 version at Web Archive: click here

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